REMARKS

Claims 6, 7, 9, 16-18 and 175-184 are pending in the subject application. By this Amendment, applicants have amended claims 6, 16, 175, 176, 182 and 183. The amendments to claims 6, 16 and 176 have been made in a manner consistent with recommendations by the Examiner to characterize the binding of claimed antibodies to TIP-2. The amendments to claims 6, 16 and 176 are supported in the specification as filed at, *inter alia*, page 173, lines 20-27 and page 175, line 34 to page 176, line 5, and thus do not raise any issue of new matter. The amendments to claims 175, 182 and 183 are merely to correct an informality. Accordingly, upon entry of this Amendment, claims 6, 7, 9, 16-18 and 175-184 will still be pending.

Allowed Claims

Applicants acknowledge with appreciation the Examiner's statement on page 11, item 11 of the Office Action that claims 7, 9, 17 and 18 are in condition for allowance.

The Claimed Invention

This invention provides monoclonal antibodies which specifically bind and form a complex with TIP-2 located on the surface of human cancer cells expressing TIP-2.

The subject monoclonal antibodies are based on applicants' *surprising discovery* that TIP-2 is uniquely associated with certain cancer cells. Prior to applicants' discovery, TIP-2, although known, had no known precise physiological role and no known association with cancer.

Rejections under 35 U.S.C. §103(a)

Claims 6 and 16

The Examiner rejected claims 6 and 16 under 35 U.S.C. §103(a) as allegedly unpatentable over De Vries et al. (PNAS 95: 12340-12345, 1998) and Rousset et al. (Oncogene 16: 643-654, 1998) and as evidenced by the specification, and further in view of Campbell (Monoclonal Antibody Technology, Elsevier Science Publishers, pages 1-32, 1986) and Harlow et al. (Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory, page 322, 1988).

The Examiner asserts that because both De Vries et al. and Rousset et al. specifically teach the PDZ domain of the TIP-2 antigen and its importance to its function and binding to other polypeptides, it would have been obvious to make antibodies to this part of the protein because this region is important for interactions with other proteins, and antibodies to this region could be used for monitoring binding. The Examiner also stated that the PDZ domain is identified in the prior art and that due to the allegedly indefinite nature of the term "extracellular domain," and lacking a definition in the specification as to the amino acids that are encompassed by that phrase, an antibody to the PDZ domain meets the limitations of the claims. The Examiner further stated that the C terminus is also identified as being important in De Vries et al. and Rousset et al. and as such one would have motivation to make an antibody to this region because it is important for binding with other molecules. The Examiner contended that, for the same reasons it would have been obvious to make an antibody to the PDZ domain, it would also have been obvious to make an antibody to the C terminus. The Examiner concluded that the invention as a whole was therefore *prima facie* obvious to one of ordinary skill in the art

at the time the invention was made, as evidenced by the references.

In response, applicants respectfully traverse the Examiner's rejection of claims 6 and 16 under 35 U.S.C. §103(a). Under 35 U.S.C. §103(a):

> (a) [a] patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Under M.P.E.P. §2142, the Examiner bears the initial burden of factually establishing a *prima facie* case of obviousness, and to do so, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge of a skilled artisan, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art reference, or references when combined, must teach or suggest all the claim limitations.

Applicants stress that the generic statement in Campbell, i.e., that "[i]t is customary now for any group working on a macromolecule to both clone the genes coding for it and make monoclonal antibodies to it (sometimes without a clear objective for their application)," does not provide "motivation" for one skilled in the art to raise monoclonal antibodies against the TIP-2 protein. Rather, applicants contend that in making such a statement, Campbell merely identifies an experimental tool that is used, but by no means obligatory, in studying a macromolecule. The Federal Circuit has specified that there must be "clear and

particular" actual evidence of a motivation, teaching or suggestion to modify prior art (*see, e.g., Teleflex, Inc.* v. *Ficosa*, 299 F.3d 1313, 1334, Fed. Cir. 2002; *Ruiz* v. *A.B. Chance Co.*, 234 F.3d 654, 665, Fed. Cir. 2002; *In re Dembiczak*, 175 F.3d 994, 999, Fed. Cir. 1999). Applicants submit, therefore, that the generic statement in Campbell relied upon by the Examiner does not meet the "clear and particular" standard for motivating the specific set of experiments which led to the isolation of monoclonal antibodies that bind to distinct regions of a tumor-associated antigen. As M.P.E.P. §2143.01 notes, the mere fact that references <u>can</u> be combined does not render the resultant combination obvious unless the prior art also suggests the *desirability* of the combination. The *desirability* of a combination is a fundamentally different notion than the mere *possibility* or even *commonality* of a combination. Applicants respectfully submit, therefore, that the Examiner has failed to show the desirability of combining the cited teachings and has, at most, shown the mere possibility of combining these teachings. Thus, the Examiner has failed to meet the first requirement for establishing a *prima facie* case of obviousness.

Applicants also wish to comment on a point made by the Examiner regarding his reliance on the Campbell reference. The Examiner responded to applicants' citation of *In re Deuel*, 51 F.3d 1552 (Fed. Cir. 1995) to support their argument that a teaching of a protein and a general experimental approach involving making antibodies cannot reasonably be construed as making obvious a monoclonal antibody that binds to a distinct domain of the protein absent a specific motive. In doing so, the Examiner asserted that *Deuel* is concerned with a specific claimed DNA sequence and does not apply to the subject claims relating to antibodies.

In response, applicants maintain that notwithstanding that this

application claims antibodies, *Deuel* nonetheless underscores the fact that the Examiner's reliance on Campbell is incorrect. Based on Campbell's statement discussed above, the Examiner concluded that because TIP-2 was previously identified, the making of antibodies to it would have been obvious, as it was "customary" for any group working on a macromolecule to make antibodies to it. However, according to Campbell, it was also customary for any group working on a macromolecule to clone the genes coding for it. Applicants contend that the Examiner's logic would lead to the conclusion that the gene coding for a known protein would necessarily be obvious.

Applicants cited *Deuel* to show that this conclusion regarding a claimed gene, predicated on Campbell, is incorrect, and to thereby show that the Examiner's conclusion regarding antibodies, also based on Campbell, is misguided. As *Deuel* states, "[a] general incentive does not make obvious a particular result, nor does the existence of techniques by which these efforts can be carried out." *In re Deuel*, F.3d 1552, 1559. Again, applying this principle to the subject invention, applicants maintain that mere availability of techniques and a generalization about common protocols do not suffice to make the antibodies of this invention obvious.

Claims 6 and 16 are directed to monoclonal antibodies that specifically bind to TIP-2 antigen located on the surface of human cancer cells. Applicants note that there is, however, no teaching in the prior art of TIP-2 either being associated with malignant transformation of human cells or being located on the surface of cancer cells. Applicants contend, therefore, that the Examiner has also failed to meet the third requirement for establishing a *prima facie* case of obviousness since the prior art references, when combined, do not teach or suggest all the claim limitations.

The Examiner attempted to address this point by asserting that although the claims require TIP-2 to be on the surface of a tumor cell, it is obvious that the antibodies produced by the combination of references would bind to TIP-2 and, since TIP-2 is on the surface of the tumor cells, the antibodies would obviously bind, and one would have a reasonable expectation of success that the antibodies would bind to TIP-2 since that was the antigen against which the antibodies were raised. However, in arriving at this conclusion, the Examiner has fallen "victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher." *In re Dembiczak*, 175 F.3d at 999 (Fed. Cir. 1999). Consistent with the Federal Circuit's repeated admonitions against hindsight analysis in obviousness determinations, M.P.E.P. §2142 notes that measuring the claimed invention against the standard of 35 U.S.C. §103(a) requires the Examiner to step backwards in time and into the shoes worn by the hypothetical "person of ordinary skill in the art" at the time when the invention was unknown and just before it was made. In view of all the factual information, the Examiner must than make a determination whether the claimed invention "as a whole" would have been obvious at that time to that person. Knowledge of applicants' disclosure must be put aside in reaching this determination and impermissible hindsight, while difficult to avoid, must be avoided.

On the basis of these guidelines, applicants respectfully submit that if knowledge of their disclosure were put aside, one of ordinary skill in the art would not have found it obvious, at the time the invention was made, to make the whole invention, i.e., to make antibodies to TIP-2 that would bind to specific regions of this protein located on the surface of human cancer cells. This is true since the surface location of TIP-2 on human cancer cells – indeed, the very association of TIP-2 with cancer cells – is known only from applicants' disclosure.

It is further stressed that the Examiner has not identified a teaching of TIP-2 antibodies produced by anyone other than applicants, even though TIP-2 was identified at least five years ago. Applicants submit that this failure by others to make antibodies to TIP-2 underscores the nonobviousness of the claimed antibodies. As the Supreme Court has made clear:

> Such secondary considerations as commercial success, long felt need, failure of others, etc., might be utilized to give light to the circumstances surrounding the origins of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18.

Applicants note that the Federal Circuit has emphatically and repeatedly held that objective evidence ("secondary considerations") of nonobviousness must always be taken into account. See, for example, *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986) ("Objective evidence such as commercial success, failure of others, long felt need, and unexpected results must be considered *before* a conclusion on obviousness is reached and is not merely 'icing on the cake' as the district court stated at trial."); *Ruiz* v. *A.B. Chance Co.*, 234 F.3d 654, 667 (Fed. Cir. 2002); "Our precedents clearly hold that secondary considerations, when present, must be considered in determining obviousness."); *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983) ("[E]vidence of secondary considerations may often be the most probative and cogent evidence in the record ... It is to be considered as part of all the evidence, not just when the decisionmaker remains in doubt after reviewing the art."). In light of the importance of secondary considerations in assessing nonobviousness, applicants maintain that the failure of others to produce antibodies to TIP-2 more than five years after the identification of this protein contradicts the Examiner's position that applicants' production of TIP-2 monoclonal antibodies would have been obvious.

For the above reasons, applicants maintain that the Examiner has failed to satisfy both the first and third criteria for establishing a *prima facie* case of obviousness, and that secondary considerations support a finding of nonobviousness. Thus, the Examiner's rejection of claims 6 and 16 as allegedly obvious is without merit.

Claims 175-180 and 182-184

The Examiner rejected claims 175-180 and 182-184 under 35 U.S.C. §103(a) as allegedly unpatentable over De Vries et al. (PNAS 95: 12340-12345, 1998) and Rousset et al. (Oncogene 16: 643-654, 1998), and as evidenced by the specification, and further in view of Campbell (Monoclonal Antibody Technology, Elsevier Science Publishers, pages 1-32, 1986), Harlow et al. (Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory, page 322, 1988), Adair et al. (WO 91/09967, published 7/11/91), Green et al. (Nature Genetics 7: 13-21, 1994) and Wei et al. (U.S. Patent No. 6,455,040, with priority to 5/99).

The Examiner stated that the claims recite a kit for detecting the TIP-2 cancer cells comprising a solid support with an anti-TIP-2 antibody that binds the same domain as 27.F7 or 27.B1 and a detectably labeled antibody labeled with a radioactive isotope, wherein the antibody is a monoclonal, humanized or human antibody. The Examiner also stated that for this rejection, the intended use for detection of cancer cells is given no patentable weight.

According to the Examiner, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a kit comprising an antibody to TIP-2, which is a humanized or chimeric or human antibody to the protein of De Vries et al. and Rousset et al., because 1) Rousset et al.

teach that the TIP-2 protein interacts with the HTLV-1 Tax oncoprotein which has been established to be associated with induction of tumors in transgenic mice, and because TIP-2 is a human protein that interacts with HTLV-1; 2) Green et al. teach methods of producing human antibodies that reduce immunogenicity when compared to mouse antibodies in treating human diseases; 3) Adair et al. teach methods comprising humanized and chimeric antibodies for therapy in humans to reduce immunogenicity in humans as compared to using mouse antibodies; 4) Wei et al. teach kits comprising solid supports with antibodies and assays for detection of antigens using the kits and labeled antibodies; and 5) Harlow et al. also teach the use of labeled antibodies for detection. The Examiner stated that since the TIP-2 protein is associated with an oncoprotein, it would thus have been *prima facie* obvious to produce a human, humanized or chimeric antibody to TIP-2 and produce a kit comprising the antibody on a solid support and a second labeled antibody.

The Examiner also stated that although the claims recite a kit, no positive recitation of the kit's ingredients or elements distinguishes the claims over the references, and therefore, the references read on the claimed kit. The Examiner stated that, further, it is a well-known convention in the art to place the recited elements in a kit for the advantages of convenience and economy, and methods of detectably labeling antibodies and derivatives thereof also were well known and available to the ordinarily skilled artisan. Thus, according to the Examiner, the claimed subject matter is considered obvious over the prior art, absent sufficient factual evidence to the contrary. The Examiner concluded that the invention as a whole was therefore *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the cited references.

In response, applicants respectfully traverse the Examiner's rejection of claims 175-180 and 182-184 under 35 U.S.C. §103(a).

As noted earlier, to establish a *prima facie* case of obviousness, the Examiner must demonstrate that, first, one of ordinary skill in the art would have been motivated to modify or combine the teachings of the cited references at the time of the invention; second, there must be a reasonable expectation that the claimed invention would succeed; and third, the cited references, when combined, must teach or suggest every element of the claim. Applicants have argued above that the Examiner has failed to meet the first and third requirements for establishing a *prima facie* case of obviousness regarding the claimed antibody, and applicants incorporate herein by reference those remarks in responding to the rejection of claims 175-180 and 182-184.

Moreover, assuming solely for the sake of argument that the claimed antibodies were obvious, applicants maintain that the claimed kits still would not have been obvious, and that the Examiner's assertion to the contrary is without merit.

The claimed kits comprise not only a probe comprising immobilized anti-TIP-2 antibody or fragment but also a means for determining the presence of probe/TIP-2 complex. Moreover, the kits are expressly for detecting the presence of TIP-2-bearing cancer cells in a sample. The cited references, in combination, fail to teach each and every element of the claimed kits in that they do not teach anti-TIP-2 antibodies, fragments thereof, and a means for detecting an antibody/TIP-2 complex. The references also do not teach the existence of TIP-2 on cancer cells, let alone the detection of these cells in a sample. Such detection, contrary to the Examiner's position, is indeed an element of the claims, and must be given weight when considering the nonobviousness of these claims.

Indeed, applicants' discovery of TIP-2's association with cancer cells was the very motivation for making these kits. It exhausts credulity to think that a kit for detecting TIP-2 on a cell or otherwise would be envisioned absent any understanding of its precise physiological role or its association with cancer cells. Thus, the cited references also fail to create a motivation to combine their teachings or a reasonable expectation that the claimed kits would work. To maintain otherwise constitutes hindsight.

Applicants maintain that since the cited art fails to teach all elements of the invention, a motive to combine or a reasonable expectation of success, the Examiner has failed to set forth a *prima facie* case of obviousness. Accordingly, applicants maintain that claims 175-180 and 182-184 satisfy the requirements of 35 U.S.C. §103(a), and request that the Examiner withdraw this rejection.

Rejections under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 6, 16, and 176-184 under 35 U.S.C. 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The Examiner stated that the term "domain" or "extracellular domain" has not been defined in the specification in relation to the TIP-2 protein. The Examiner further stated that whereas the term "domain" may refer to a portion of the polypeptide, it was not known what region or which amino acids were defined in the "extracellular domain." The Examiner also stated that because the specification does not define any specific region or indicate whether TIP-2 has an "extracellular domain," one cannot determine the metes and bounds of the claims.

In response, applicants respectfully traverse the Examiner's rejection of claims 6, 16 and 176-184 under 35 U.S.C. §112, second paragraph. Applicants note that claims 6, 16 and 176, as amended, do not recite the terms "domain" or "extracellular domain." Applicants therefore respectfully request that the Examiner reconsider and withdraw his rejection of claims 6, 16 and 176, and claims 177-184 which depend from claim 176, under 35 U.S.C. §112, second paragraph.

Rejections under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 6, 16, and 176-184 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Examiner stated that while the specification does disclose the binding to the surface of cancer cells by 27.B1 and binding of 27.B7 intracellularly to fixed cells, there is nothing in the specification to define a "domain" or an "extracellular domain" or "intracellular domain." According to the Examiner, the terms "domain" and "extracellular domain" in the claims are therefore new matter. The Examiner suggested that applicants amend the claims to recite that 27.B1 binds to TIP-2 on the surface of cancer cells expressing TIP-2 and that 27.F7 binds intracellularly to TIP-2 on fixed cells as recited in the specification on page 173, lines 22-25.

In response, applicants respectfully traverse the Examiner's rejection of claims 6, 16 and 176-184 under 35 U.S.C. §112, first paragraph. Nevertheless, to expedite prosecution of the subject application and without conceding the correctness of the

Examiner's position, applicants have amended claims 6, 16 and 176 in keeping with the Examiner's recommendations. Applicants respectfully submit that claims 6, 16 and 176, as amended, and claims 177-184 which depend from claim 176, satisfy the requirements of 35 U.S.C. §112, first paragraph.

The Examiner also rejected claim 16 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. According to the Examiner, claim 16 contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Examiner stated that claim 16 has been amended to recite "binds the same extracellular domain of TIP-2 as does monoclonal antibody 27.F7," with support for the limitation allegedly to be found at pages 173, 175 and 176. The Examiner also stated that whereas the recited pages show support for the 27.B1 antibody binding to TIP-2 on the surface of cancer cells, the 27.F7 antibody is reported to bind intracellularly to fixed cells. The Examiner stated that applicants are required to point to specific support for the limitation in the specification as originally filed or remove it from the claim.

In response, applicants note that the error identified by the Examiner has been corrected in claim 16, as amended. Applicants therefore request that the rejection of claim 16 under 35 U.S.C. §112 be withdrawn.

Conclusion

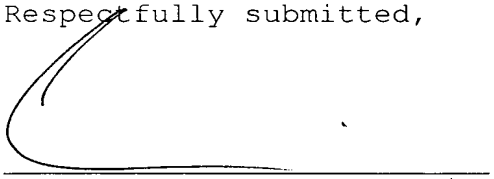
In view of the remarks made herein, applicants respectfully request that the Examiner reconsider and withdraw the various

grounds of objection and rejection set forth in the October 16, 2003 Office Action and earnestly solicit allowance of all claims pending in the subject application.

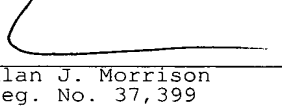
If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450 Alexandria, VA 22313-1450.



1/9/04

Alan J. Morrison
Reg. No. 37,399

Date

John P. White
Registration No. 28,678
Alan J. Morrison
Registration No. 37,399
Attorneys for Applicant
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400